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# Efficacy of desmopressin in patients with multiple sclerosis suffering from bladder dysfunction: a meta-analysis

Bosma R, Wynia K, Havlíková E, De Keyser J, Middel B. Efficacy of desmopressin in patients with multiple sclerosis suffering from bladder dysfunction: a meta-analysis.

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**Objectives** – The current review evaluates the safety and efficacy of desmopressin in patients with multiple sclerosis (MS) who suffer from both daytime and nocturnal voiding frequency and from incontinence. **Materials and methods** – A literature search was carried out looking for studies published between 1990 and 2003 which evaluated desmopressin in MS patients with bladder dysfunction. **Results** – The grand total mean effect sizes show the following estimates of clinical relevant differences: desmopressin has a moderate effect on the number of voids during the day or during the night over a period of 6 h after taking the drug. A large effect associated with the use of desmopressin was detected by the mean difference in urine volume (ml) in 6 h. A small effect was detected in the mean 24-h urine volume. Serum sodium levels were combined with plasma osmolality in some studies and were found to be not significantly affected by desmopressin treatment.

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**Key words:** bladder dysfunction; desmopressin; multiple sclerosis; urinary frequency

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Bladder dysfunction is a very common problem in patients with multiple sclerosis (MS). Approximately 90% of MS patients have bladder problems during the course of the disease, including increased voiding frequency, urgency problems and incontinence (1–3).

Bladder problems are very distressing and affect many important aspects of everyday life, such as social inconvenience, for example in the work situation, during a theatre visit, a meeting or other social occasions. However, the physical and emotional health status of MS patients is also affected by motor problems and fatigue and the combination of these symptoms may increase psychological distress and problems in coping with nocturia, daytime frequency and incontinence. In addition, these problems may increase the burden on the patient's partner or carer. The reduction of voiding frequency and incontinence are therefore relevant therapeutic goals that may improve the patient's perceived health status and quality of life. Administration of desmopressin would appear to be an effective and well-tolerated method to reduce the

voiding frequency and incontinence in MS patients with varying neurological disability and handicapping micturition problems. Desmopressin (1-desamino-8-D-arginine vasopressin) is a synthetic analogue of the anti-diuretic hormone vasopressin. The drug increases the resorption of water in the collecting tubules of the kidneys. The safety and efficacy of this drug was shown in patients with diabetes insipides and nocturnal enuresis (4, 5). Some studies have evaluated the effect of desmopressin in patients with MS (1, 6–9). The current review evaluates the safety and efficacy of desmopressin in patients with MS who suffer from both daytime and nocturnal voiding frequency and from incontinence.

## Materials and methods

A literature search was carried out looking for studies published between 1990 and 2003 which evaluated desmopressin in MS patients with bladder dysfunction. Electronic databases such as Medline, Cinahl, Embase, Psycinfo and Picarta

were employed using the search terms 'multiple sclerosis' and 'desmopressin'.

The studies had to meet four criteria for inclusion. First, they had to have been published in English or Dutch. Secondly, the design had to be a clinical trial or a randomized clinical trial. Thirdly, only MS patients with bladder dysfunction could be the subject of evaluation of desmopressin effectiveness. Finally, the studies had to have only used one or more of the following outcome parameters: voiding frequency, incontinence, urine volume and/or serum sodium level. Only statistically significant differences in outcome parameters between treatment with desmopressin and control conditions were used to evaluate the effectiveness of treatment by pooling the effect size (ES) estimates (10). The ES was estimated by calculating the mean difference between the placebo and desmopressin groups after the intervention, and divided by the pooled standard deviation (SD) of the post-treatment outcome measure of the placebo and desmopressin group (11). Cohen's threshold values for interpretation of the magnitude of differences between treatment and control groups were used: 'trivial effect' ( $ES \leq 0.20$ ), 'small effect' ( $ES \geq 0.20 < 0.50$ ), 'moderate effect' ( $ES \geq 0.50 < 0.80$ ) and 'large effect' ( $ES \geq 0.80$ ) (12).

## Results

The use of the keywords in the literature search resulted in 57 publications. After applying the inclusion and exclusion criteria, the selection yielded five studies which were appropriate for a meta-analysis (1, 6–9) with a randomized double-blind placebo-controlled, cross-over design. Desmopressin was administered both as an oral and nasal drug during the daytime and at night. The

studies comprised 115 MS patients with increased frequency of voiding/incontinence episodes. Only 98 patients (85%) were included for statistical analysis: 70 women (71%) and 28 men (29%) with a mean age of 49 years (range 24–70). Table 1 summarizes the results of the clinical outcome parameters which the studies have in common.

### Frequency and urine volume

Desmopressin increases the resorption of water and therefore has a negative effect on the urine volume, which also has an effect on the voiding frequency and incontinence. All the studies evaluated mean voiding frequency, either 6 h after desmopressin during the day (between 8.00 and 14.00 h), or after desmopressin was used at night (bedtime). A statistically significant lower voiding frequency in the first 6–8 h after the administration of desmopressin was detected in all of the studies. The mean difference in the voiding frequency between the placebo and desmopressin groups ranged from 0.5 to 0.7 during the day, and from 0.5 to 1.0 during the night. Three studies evaluated the urine volume in the first 6 or 8 h or during the night after taking the drug. All three studies detected statistically significant differences in urine volume between the desmopressin and placebo groups. Furthermore, two studies evaluated 24-h urine volumes, but no statistically significant differences between the desmopressin and placebo groups were detected.

### Serum levels

No statistically significant differences were detected between the placebo and desmopressin groups in any of the studies which evaluated the levels of serum sodium. Kinn and Larsson (9) did not present any

**Table 1** Effectiveness of desmopressin as a treatment for urgency and incontinence in five experimental studies among patients with multiple sclerosis (statistically significant differences are printed in bold)

	Eckford et al. (6)		Hoverd and Fowler (8)		Fredrikson (7)		Kinn and Larsson (9)		Valiquette et al. (1)	
	Desmopressin (n = 31)	Placebo (n = 31)	Desmopressin (n = 22)	Placebo (n = 22)	Desmopressin (n = 22)	Placebo (n = 22)	Desmopressin (n = 12)	Placebo (n = 12)	Desmopressin (n = 11)	Placebo (n = 11)
Mean no. of voids in 6 h (SD)			<b>2.4 (0.9)</b>	<b>3.1 (1.4)</b>	<b>2.6 (1.0)</b>	<b>3.1 (1.0)</b>	<b>2.4 (1.0)</b>	<b>3.1 (1.1)</b>		
Mean no. of night-time voids (SD)	<b>1.27 (0.8)</b>	<b>1.74 (0.66)</b>							<b>1.09 (1.10)</b>	<b>2.07 (1.13)</b>
Mean urine volume in 6 h or night, ml (SD)	<b>341 (134)</b>	<b>502 (201)</b>	<b>246 (99)</b>	<b>342 (166)</b>			<b>325<sup>1</sup></b>	<b>440</b>		
Mean urine volume in 24 h, ml (SD)	<b>1372.1 (478.4)</b>	<b>1510.5 (483.2)</b>	1218 (455)	1272 (482)						
Mean serum sodium, mmol/l (SD)	140.2 (4.8)	141.5 (3.2)	139.2 (3.3)	139.7 (3.0)	140 (3.1)	141 (3.2)			139.8 (1.4)	140.5 (1.7)

<sup>1</sup>According to the authors this difference was statistically significant. However, as no standard deviations were published, no effect size estimates could be calculated.

statistical information regarding the level of serum sodium; however, they concluded that blood sample outcomes remained stable during the study.

#### Side-effects

Most of the reported side-effects are related to hyponatraemia. In general these symptoms were assessed as being mild. Patients (0–8%) reported fluid retention or side-effects related to fluid retention. Headache was seen in 3–4% of the research population. Other mild symptoms reported included nausea, swollen ankles, abdominal aches, increased hesitancy, but most of these symptoms vanished spontaneously.

#### Patients' preference

After pooling the data from the studies, 72% of 81 patients preferred the period in which they were treated with desmopressin to the period in which they were treated with a placebo. Fredrikson (7) found that 68% of patients had a preference for the active treatment phase, whilst others researchers (6, 8, 9) found 65, 80 and 75%, respectively. Furthermore, Valiquette et al. (1) reported that 82% of the patients requested a continuation of desmopressin after the trial. Furthermore, patients included in their study reported that desmopressin treatment restored their normal sleep patterns, which resulted in dramatic improvements in their quality of life (1).

#### Clinically relevant differences

The problem of testing differences between placebo and desmopressin groups with a null hypothesis is that the outcome has to be sufficiently different from what would have been expected on the basis of chance ( $P < \alpha$ ).

However, statistically significant results do not imply that the effects of each study were important, as trivial differences between experimental groups are likely to be statistically significant in large samples.

Effect size indices were used in order to give meaning to the magnitude of these statistically significant differences. These indices standardize the differences between mean scores to adjust for arbitrary units of measurement in order to produce a measure in standard deviation units rather than in the units of the original scale. In order to assess the clinical relevance of the differences in outcome between placebo and desmopressin groups, the results of the selected studies from Table 1 were aggregated by pooling the ES of each study into a grand mean ES index.

Table 2 shows the grand mean ES estimates from the sample values found in the five studies which compared the outcome in the placebo and desmopressin groups (13). The grand total mean ES show the following estimates of clinical relevant differences: desmopressin has a moderate effect on the number of voids during the day or during the night over a period of 6 h after taking the drug. A large effect associated with the use of desmopressin was detected by the mean difference in urine volume (ml) in 6 h. A small effect was detected in the mean 24-h urine volume. Serum sodium levels were combined with plasma osmolality in some studies and were found to be not significantly affected by desmopressin treatment.

#### Conclusion/discussion

To our knowledge, only five studies have evaluated the effectiveness and safety of desmopressin in patients with MS in an RCT study design during the period 1990 and 2003. All studies used self-assessment of the voiding frequency and side-effects.

Voiding frequency and/or incontinence is significantly decreased in the first 6–8 h or at night in the group of patients receiving desmopressin. This is probably the most important factor for the patients. During the night the voiding frequency determines the extent of a disturbed sleeping pattern. Correspondingly, urinary volume significantly and substantially ( $ES > 0.80$ ) decreased in this period. Most patients preferred the treatment with desmopressin even though the reduction in voids was small. The question is whether or not this reduction is clinically relevant. Reported side-effects mainly correspond with hyponatraemia and fluid retention. In general, the side-effects were mild. Hyponatraemia, however, can have serious consequences. It is, on the one hand, important to stress the possible risk of hyponatraemia and its symptoms and to emphasize that it should be used only once a day. On the other hand, the emphasis should not be so great that the patient's compliance is affected negatively as this may be problematic in MS patients with cognitive impairments. Patients with cardiovascular and renal diseases,

**Table 2** Grand total effect size (ES) estimates

Outcome measures	Range	ES	Effect
Mean no. of voids in 6 h	0.50–0.67	0.60	Moderate
Mean no. of night-time voids	0.64–0.88	0.77	Moderate
Mean urine volume in 6 h (ml)	0.71–0.95	0.83	Large
Mean urine volume in 24 h (ml)	0.11–0.29	0.20	Small

hypertension, diabetes and hepatic diseases should not be treated (1, 9).

It could be argued that the use of desmopressin influences the incidence of urinary tract infections. The higher urinary concentration may provide less favourable conditions for bacterial growth. Longer intervals between voids, however, increase bacterial growth. Two studies evaluated the incidence of urinary tract infections and found that it ranged from 6 to 23%.

Most studies refer to indications for administration of desmopressin in MS patients with lower urinary tract dysfunction. In general the indications are advanced urgency and urinary leakage due to detrusor hyperreflexia (6, 7, 9). In fact desmopressin is a novel approach to the management of lower urinary tract dysfunctions in MS. Well-known measures are the application of fluid restriction (in order to minimize bladder filling), anticholinergic drugs (to relax the bladder musculature and to increase bladder capacity), and intermittent self-catheterization (to empty the bladder at fixed time-intervals). Consequently the studies vary in the indications for application of desmopressin as an additional measure to well-known methods in special situations: 1) in case of socially handicapping bladder dysfunction or in case of resistance to other drugs (anticholinergics) (7); 2) when anticholinergic therapy is unfavourable because of significant adverse effects (1) and 3) to gain symptomatic control of nocturnal urine production rates (1, 6).

Most studies evaluated the efficacy of 10 or 20 µg of desmopressin. One study was found in which incrementally increasing doses of 20, 40 and 60 µg were compared (14). This study showed that doses of > 20 µg cannot be recommended, as they had no immediate advantages over a 20-µg dose in reducing urinary production or increasing urinary osmolality. Furthermore, there was a potentially worrying trend towards hyponatraemia on completing a 60- µg dose (14).

The studies included in our literature search evaluated the short-term effect of desmopressin. Two studies evaluating the long-term effect of desmopressin were also found. One retrospective study covered an average follow-up of 2.4 years (15). A substantial number of the patients (74%) reported a stable effect of desmopressin.

In another study (16), in which only eight patients were included, Valiquette et al. reported a stable effect during a mean period of 13 months (1). These studies indicate that desmopressin may be effective over a longer period of time.

Three studies referred to pros and cons of oral and nasal administration of desmopressin in MS

patients with bladder dysfunction: Kinn and Larson (9) referred to difficulties in nasal administration for patients with muscular and motor dysfunctions. Eckford et al. (6), on the other hand, found that despite severely compromised manual dexterity patients were able to self-administer the drug. Fredrikson (7) referred to possible treatment failures in nasal application due to improper spraying technique and reduced nasal absorption. Possible disadvantages of oral administration are the slower onset of action compared to intranasal application and the oral dose is more than 10 times the dose used for intranasal administration (9).

Desmopressin can play a significant role in the health-related functional status of MS patients, especially those patients with a high frequency both during daytime, on special occasions and at night, for an undisturbed sleep. This therapy can be greatly beneficial in this group of patients, reducing the number of voids, for example, by 50%. Other therapies are first recommended as the costs are rather high and the clinical relevance is limited. When prescribing desmopressin, attention should be paid to hyponatraemia. It is clear that the long-term effects, effects on urinary tract infections and the hours of undisturbed sleep need further investigation.

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